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10/532,868	04/28/2005	Francois Andre	03715.0147	3789
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413			EXAMINER RIGGS II, LARRY D	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/532,868

**Applicant(s)**

ANDRE ET AL

**Examiner**

LARRY D. RIGGS II

**Art Unit**

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 December 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 27-30 and 33-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 27-30 and 33-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S5108)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

Applicant's amendments filed 17 December 2008 are acknowledged and entered.

***Status of Claims***

Claims 1-26, 31, 32 and 40-67 are cancelled. Claims 27-30 and 33-39 are currently pending and under consideration.

***Withdrawn Rejections/Objections***

The objection of the disclosure in the Office action mailed 09 July 2008 is withdrawn in view of the amendments filed 17 December 2008.

The objection to claims 27, 28, 30 and 33-35, in the Office action mailed 09 July 2008 is withdrawn in view of the amendments filed 17 December 2008.

The rejection of claims 27-30 and 33-39 under 35 U.S.C. §112, Second Paragraph, in the Office action mailed 09 July 2008 is withdrawn in view of the amendments and arguments filed 17 December 2008.

The rejection of claims 27-30 and 33-39 under 35 U.S.C. §101, in the Office action mailed 09 July 2008 is withdrawn in view of the recent en banc decision regarding Bilski.

The rejection of claims 27, 28 and 35 under 35 U.S.C. 103(a) over Chang et al. in view of Di Nola et al. and further in view of Mager, in the Office action mailed 09 July 2008 is withdrawn in view of the arguments filed 17 December 2008.

The rejection of claim 30 under 35 U.S.C. 103(a) over Chang et al. in view of Di Nola et al. further in view of Mager and further in view of Case et al., in the Office action mailed 09 July 2008 is withdrawn in view of the arguments filed 17 December 2008.

### ***Claim Objections***

This objection is newly applied in-part in light of the amended claims and is repeated in-part from the previous Office action.

Claims 27, 28, 30 and 33 are objected to because of the following informalities:

Line 3 of step B) of the instant claim 27 provides "wherein some the other atoms are mobile". The Examiner suggests adding "the spatial position" and "of" to the limitation resulting in "wherein the spatial position of some of the other atoms is mobile", for grammatical correctness.

i) and ii) of steps B and D of the instant claim 27 are followed by periods. The Examiner suggests removing all periods throughout the instant claim except the final period.

Line 2 of the instant claim 28 provides "N-C.alpha.-CO". The Examiner suggests removing the periods on either side of the limitation "alpha".

Line 2 of the instant claim 30 provides "A j comprises forces lined to a. the distance..." The Examiner suggests removing "j" or removing "A" because both steps "A" and "J" are encompassed in the instant claim. Likewise, the Examiner suggests removing the extra "period" because the claim is limited to one period.

Line 1 of the instant claim 33 provides "step F o is performed..." The Examiner suggests removing "o" because step "o" has been cancelled.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The instant rejection is newly applied in light of recently amended claims.

Claims 27-30 and 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "optionally repeating step k" in line 1 of step C). There is insufficient antecedent basis for this limitation in the claim because step k has been eliminated in the instant claim.

Claim 30 recites the limitation "in step A j comprises" in lines 1-2. The metes and bounds of the limitation are unclear because the instant claim 27 contains both steps "A" and "J" from which the instant claim 30 depends. One skilled in the art would be unclear which step the instant claim 30 further limits.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The instant rejection is newly applied in light of the recent en banc decision regarding Bilski.

Claims 27-30 and 33-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The recent en banc decision regarding Bilski v. Warsaw (2008) set forth that a process is patent-eligible if (1) it is tied to a particular machine or apparatus or (2) it transforms a particular article into a different state or thing. Further, the recent decision in Comiskey (2009) confirmed the opinion set forth in Bilski of the prohibition pre-empting an abstract idea or mental process in a claim. The revised Comiskey decision further reiterated the president set forth in Richman, 563 F.2d 1026, 1030 (CCPA 1977) wherein the court held the application unpatentable because "if a claim [as a whole] is

directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory."

The instant claims are drawn to a method for performing restrained dynamics docking of a substrate on an enzyme. The instant claims are drawn to the abstract process steps of determining a force field and simulating the presence of the enzyme in the force field, minimizing the potential energy when some of the enzymes atoms' are mobile, optionally repeating a step to obtain other potential energy minima, minimizing potential energy when all the enzyme atoms' positions are mobile, simulating at 0 degrees Kelvin the presence of a substrate next to the enzyme, optionally generating a molecular dynamics simulation on the substrate and enzyme, generating some constraints on the substrate, generating a molecular dynamics simulation on the substrate and enzyme with the substrate constraints, optionally generating a molecular dynamics simulation on the substrate and enzyme without constraints and generating a result corresponding to a simulation of the docking of the substrate on the enzyme in a readable format.

The instant claims do not recite or inherently involve any transformation of an article, therefore the Examiner must determine if the instant claims have a tie to a particular machine or apparatus. Instant claims do not recite any limitation that ties the recited abstract process to any particular machine or apparatus. A computer-assisted method is just a method. There is no particular machine or apparatus.

Further, displaying a simulation of the docking of a substrate to an enzyme is an insignificant post-solution activity. Nominal or token recitations will not suffice, E.g.

displaying, inputting, obtaining, See Ex parte Langemyr (May 28, 2008). Applicants are cautioned against introduction of new matter in an amendment.

### ***Response to Arguments***

Applicant's arguments filed 17 December have been fully considered and are moot in light of the new grounds of rejection set forth above.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation



under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant rejection is newly applied with new art and with current art of record.

Claims 27-29, 33-35 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al., (Biochemistry, 2000, 39, 2484-2498) in view of Guntert et al. (J. Mol. Biol., 1997, 273, 283-298) and further in view of Di Nola et al. (Proteins: Structure, Function, and Genetics, 1994, 19, 174-182).

The instant claim 27 provides a computer-assisted method for performing restrained dynamics docking of a substrate on an enzyme, a 3-D structure of said enzyme being available, comprising the steps of:

A) determining a force field, and independently simulating the presence of said enzyme in said force field,

B) minimizing the potential energy ( $E_p$ ) linked to said force field of said 3-D structure, wherein the spatial position of some atoms of said enzyme is fixed, and wherein the spatial position of some of the other atoms are mobile, by allowing mobility of the mobile atoms, by

- i) simulating an increase in temperature (in order to give kinetic energy),
- ii) and minimizing the potential energy ( $E_p$ ) linked to said force field of said 3-D structure by re-specifying the temperature as 0 Kelvin (K),

C) (optionally) repeating step k in order to obtain other  $E_p$  minima, wherein said  $E_p$  minima are such that the structure of the enzyme remains folded,

D) minimizing  $E_p$  in said force field of said 3-D structure, wherein all the atoms of the enzyme are mobile, by

i) simulating an increase in temperature (in order to give kinetic energy), and

ii) minimizing the potential energy ( $E_p$ ) linked to said force field of said 3-D structure by re-specifying the temperature as 0 degrees Kelvin (K),

E) simulating, at 0 K the presence of said substrate next to said enzyme,

F) (optionally) generating a molecular dynamics simulation on said substrate and enzyme (simulating an increase in temperature, in order to allow mobility of all the atoms),

G) generating some constraints to said substrate, in order to impose that said substrate has interaction with said enzyme, wherein said constraints are final distance constraints between some atoms of said substrate and some atoms of amino-acids present in said active site,

H) generating a molecular dynamics simulation on said substrate and enzyme, with said constraints imposed in step G,

I) (optionally), generating a molecular dynamics simulation on said substrate and enzyme without said constraints of step G; and

J) generating a result corresponding to a simulation of the docking of the substrate on the enzyme in a user readable format.

Regarding claim 27, Chang et al. shows previously available P450 3-D structures to base the CYP119 structure on, (page 2485, right column, third paragraph), and simulating the CYP119 structure in a force field using the software AMBER, (page 2486, left column, fourth paragraph). Chang et al. shows partially constrained energy minimization of both the backbone and the side chains of nonstructurally conserved regions performed using Amber 4.1 with a radius of gyration (page 2486, left column, third paragraph, page 2489, right column, third-fifth paragraphs) and unconstrained energy minimization using a nonbonding cutoff of 8 Angstroms and a distance-dependent radial dielectric performed (final distance), with all residues, structural water molecules and the resting state heme unit allowed to move in the minimization using combined steepest descent and conjugate gradient method (minimizing  $E_p$ ) to obtain the fully minimized model, (page 2486, left column, last paragraph) (meeting most limitations of A-D). Chang et al. shows increasing temperature within a simulation, (page 2486, right column, second to last paragraph). Chang et al. shows enzyme-substrate docking using program GRAMM, using substrates Putidaredoxin and FMN domain of CYP102 for the prediction of complex formation with CYP119, (page 2495, left column, last paragraph – page 2496, left column, second paragraph). Chang et al. shows final distant constraints between CYP119 and Putidaredoxin and the FMN domain of P450BM3, (Table 7), (meeting the limitations of steps G and H).

Chang et al. does not show simulating an increase in temperature followed by a decrease in temperature to 0 degrees Kelvin (steps i) and ii) within steps B and D). Chang et al. does not show simulating at 0 degrees Kelvin the presence of substrate next to the enzyme.

Guntert et al. shows molecular dynamics for protein structure calculation with the simulation starting at a high temperature followed by simulation dropping to 0 degrees Kelvin, (page 290, left column, first paragraph – right column, first paragraph; page 295, right column, second paragraph – page 296, left column, second paragraph; Figure 4).

Chang et al. and Guntert et al. do not show simulating at 0 degrees Kelvin the presence of substrate next to the enzyme.

Di Nola et al. shows a method of molecular dynamics simulation of docking of a frozen or rigid enzyme, i.e. considering the receptor as rigid and hence couple its motion strongly to a bath of very low temperature, next to a rigid substrate, i.e. it is possible to freeze the internal motion of the substrate and perform the so called "rigid docking", (page 175, left column, fifth paragraph; page 176, left column, #2). Di Nola et al. shows that the bond lengths of the substrates were kept rigid and the receptor atoms were constrained to their starting position and no intramolecular interaction in the receptor were calculated and the temperature of the receptor was kept at 10 degrees Kelvin, (page 176, left column, fourth paragraph). Likewise, Di Nola et al. also shows a molecular dynamics simulation of the phosphocholine-immunoglobulin complex at a high temperature followed by a temperature down to almost 0 degrees Kelvin, (page 176, left column, last paragraph). One skilled in the art would consider obvious that

keeping a receptor and substrate frozen, rigid or down to 10 degrees Kelvin would encompass bringing a temperature down to 0 degrees Kelvin. Di Nola et al. shows that the docking simulation was performed by taking into account all atoms of the receptor included in a sphere of 2.0 nm radius, centered at the com of the substrate in the crystal structure, with a cutoff radius of 0.8nm used for intermolecular interactions, (page 176, left column, last paragraph – right column, first paragraph; Figure 3). One skilled in the art would understand that docking simulations between receptors and substrates means that the simulations are done within a sphere of a particular radius.

Regarding claim 28, Chang et al. shows constrained energy minimization of both the backbone and side chains of nonstructurally conserved regions performed by AMBER, (page 2486, left column), then a number and duration of segments of constrained MD simulations increased, (2486, right column, second paragraph-last paragraph).

Regarding claim 29, Guntert et al. shows molecular dynamics for protein structure calculation with the simulation starting at a high temperature followed by simulation dropping to 0 degrees Kelvin, (page 290, left column, first paragraph – right column, first paragraph; page 295, right column, second paragraph – page 296, left column, second paragraph; Figure 4). The simulations of Guntert et al. are about 100K and can be simulated up to 20 nanoseconds if using a TAD run of 100 fs and 20000 TADS, (page 288, left column, last paragraph – right column, first paragraph; Figures 1 and 6)

Regarding claims 33 and 34, Di Nola et al. shows a method of molecular dynamics simulation of docking of a frozen or rigid enzyme, i.e. considering the receptor as rigid and hence couple its motion strongly to a bath of very low temperature, next to a rigid substrate, i.e. it is possible to freeze the internal motion of the substrate and perform the so called "rigid docking", (page 175, left column, fifth paragraph; page 176, left column, #2). Di Nola et al. shows that the bond lengths of the substrates were kept rigid and the receptor atoms were constrained to their starting position and no intramolecular interaction in the receptor were calculated and the temperature of the receptor was kept at 10 degrees Kelvin, (page 176, left column, fourth paragraph).

Guntert et al. shows molecular dynamics for protein structure calculation with the simulation starting at a high temperature followed by simulation dropping to 0 degrees Kelvin, (page 290, left column, first paragraph – right column, first paragraph; page 295, right column, second paragraph – page 296, left column, second paragraph; Figure 4). Gunter et al. simulations go down to 0 degrees Kelvin and One skilled in the art would consider it obvious simulate rigid receptor-substrate dockings at low temperatures such as 15-50 degrees Kelvin.

Regarding claim 35, Chang et al. shows simulation at 300 Kelvin, (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with the molecular dynamics simulation of the docking of substrates to proteins by Di Nola et al. and the simulations with zero Kelvin

by Mager because Chang et al. shows reducing temperature to obtain a fully minimized model, (2486, left column, last paragraph).

Regarding claim 38, Di Nola et al. shows the substrate phosphocholine which is a small organic compound, (page 176, left column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with temperature changes of Guntert et al. and the simulation docking of a rigid receptor next to a substrate by Di Nola et al. because Chang et al. shows lower temperatures allow one to obtain a fully minimized stable model (2496, left column, last paragraph). Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

Claims 27-30, 33-35 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al., (Biochemistry, 2000, 39, 2484-2498) in view of Guntert et al. (J. Mol. Biol., 1997, 273, 283-298) and further in view of Di Nola et al. (Proteins: Structure, Function, and Genetics, 1994, 19, 174-182) as applied to claims 27-29, 33-35 and 38, and further in view of Case et al., (AMBER User's Manual, April 20, 2002, 1-326).

The instant claim 30 depends from claim 27 with the extra limitation that wherein said force field in step A) comprises forces linked to the distance between atoms,

angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds.

Chang et al., Guntert et al. and Di Nola et al. are applied to claims 27-29, 33-35 and 38 above.

Chang et al., Guntert et al. and Di Nola et al. do not show force field in step A) comprises forces linked to the distance between atoms, angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds.

Case et al. shows force field linked to distance between atoms, angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds with the Sander module that carries out energy minimization, molecular dynamics and NMR refinements and assessing improper torsions, (pages 80 and 294).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with temperature changes of Guntert et al. and the simulation docking of a rigid receptor next to a substrate by Di Nola et al. and the force field linked to various angles, fields and forces of Case et al., because Chang et al. shows using AMBER software for molecular dynamic simulation (2486, left column, fourth paragraph). Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.



Claims 27-29 and 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al., (Biochemistry, 2000, 39, 2484-2498) in view of Guntert et al. (J. Mol. Biol., 1997, 273, 283-298) and further in view of Di Nola et al. (Proteins: Structure, Function, and Genetics, 1994, 19, 174-182) as applied to claims 27-29, 33-35 and 38, and further in view of Szklarz et al., (Journal of Computer-Aided Molecular Design, 1997, 11, 265-272).

The instant claims 36, 37 and 38 depend from claim 27 with the extra limitations that the enzyme is a mammalian or human cytochrome P450 3A, i.e. P450 3A4 and the substrate is testosterone.

Chang et al., Guntert et al. and Di Nola et al. are applied to claims 27-29, 33-35 and 38 above.

Chang et al. shows molecular dynamic simulations of P450 enzyme CYP119 based on other known P450 enzymes, (abstract, page 2487, left column, first paragraph; Tables 1, 3 and 4).

Chang et al., Guntert et al. and Di Nola et al. do not show molecular dynamic simulations of P450 3A or 3A4 and a docking simulation with testosterone substrate.

Regarding claims 36, 37 and 39, Szklarz et al. shows molecular dynamic simulations of human cytochrome P450 3A4 with substrates such as progesterone, (abstract, page 267, left column, first paragraph; page 268, right column, second paragraph; Figure 3). Szklarz et al. shows the testosterone is a known substrate of cytochrome P450 3A4, (page 265, right column, first paragraph). It would be obvious to

one skilled in the art to perform a molecular dynamic docking simulation of cytochrome P450 3A4 with the known substrate testosterone.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with temperature changes of Guntert et al. and the simulation docking of a rigid receptor next to a substrate by Di Nola et al. and the simulation of human cytochrome P450 3A4 and testosterone substrate of Szklarz et al., because Chang et al. shows molecular dynamic simulations of P450 enzyme CYP119 based on other known P450 enzymes, (abstract, page 2487, left column, first paragraph; Tables 1, 3 and 4) and one skilled in the art would consider it obvious to perform a molecular dynamic simulation of a known P450 enzyme and its known substrate. Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

### ***Response to Arguments***

Because the newly applied rejection contains art of record, applicant's arguments regarding those pieces of art will be considered. Applicant's arguments filed 17 December 2008 have been fully considered but they are not persuasive.

Applicants argue that Chang et al. and Di Nola et al. do not disclose comparing two steps of minimizing potential energy with some atoms fixed and then all atoms mobile. Chang et al. does not disclose simulating increasing temperature and then dropping the temperature to 0 degrees Kelvin. Chang et al. and Di Nola et al. do not

disclose a substrate next to the enzyme at 0 degrees Kelvin. Di Nola et al. does not disclose simulating the substrate itself but only the center of motion.

Applicants arguments are not persuasive. Chang et al. does show simulation with atoms both fixed in-part and mobile, see above. Chang et al. does show simulation with an increase in temperature, see above. Di Nola et al. shows simulating a substrate and receptor at 0 degrees Kelvin, see above. Any other limitations are supplied by the newly cited art. Limitations not shown by a single prior art reference does not mean that the cited art does not apply. Applicant is reminded that a rejection under 35 U.S.C. §103(a) may be a combination of references that when taken as a whole will make the invention obvious.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LDR/  
Larry D. Riggs II  
Examiner, Art Unit 1631

/ERIC S. DEJONG/  
Primary Examiner, Art Unit 1631